Placebo-Induced Changes in fMRI in the Anticipation and Experience of Pain

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The experience of pain arises from both physiological and psychological factors, including one’s beliefs and expectations. Thus, placebo treatments that have no intrinsic pharmacological effects may produce analgesia by altering expectations. However, controversy exists regarding whether placebos alter sensory pain transmission, pain affect, or simply produce compliance with the suggestions of investigators. In two functional magnetic resonance imaging (fMRI) experiments, we found that placebo analgesia was related to decreased brain activity in pain-sensitive brain regions, including the thalamus, insula, and anterior cingulate cortex, and was associated with increased activity during anticipation of pain in the prefrontal cortex, providing evidence that placebos alter the experience of pain.

The idea that sensory experience is shaped by one’s attitudes and beliefs has gained currency among psychologists, physicians, and the general public. Perhaps nowhere is this more apparent than in our ability to modulate pain perception. A special case of this phenomenon is placebo analgesia, in which the mere belief that one is receiving an effective analgesic treatment can reduce pain (1–5). Recently, some researchers have attributed placebo effects to response bias and/or to publication biases (6), which raises the issue of whether placebo treatments actually influence the sensory, affective, and cognitive processes that mediate the experience of pain.

One important piece of evidence that placebo effects are not simply due to response or publication bias is that such effects can be reversed by the mu-opioid antagonist naloxone (2, 3, 7), suggesting that some kinds of placebo effects may be mediated by the opioid system. However, naloxone has also been shown to produce hyperalgesia independent of placebo, in some cases offsetting rather than blocking the effects of placebo analgesia (8). Although pharmacological blockade provides suggestive evidence regarding the neurochemical mechanisms mediating placebo effects, such data do not illuminate the nature of the information-processing system that gives rise to such effects. Neuroimaging data can provide complementary evidence of how pain processing in the brain is affected by placebos and about the time course of pain processing. Identifying placebo-induced changes in brain activity in regions associated with sensory, affective, and cognitive pain processing (9) may provide insight into which components of pain processing are affected by placebo. In addition, identifying changes that occur at particular times—in anticipation of pain, early or late during pain processing—may shed light on how cognitive systems mediating expectancy interact with pain and opioid systems.

In two functional magnetic resonance imaging (fMRI) experiments (n = 24 and n = 23), we examined two hypotheses regarding the psychological and neural mechanisms that underlie placebo analgesia. Our first hypothesis was that if placebo manipulations reduce the experience of pain, pain-responsive regions of the brain should show a reduced fMRI blood oxygen level-dependent (BOLD) signal (a measure related to neural activity) during pain. Pain-responsive regions, or the “pain matrix,” include thalamus, somatosensory cortex, insula, and anterior cingulate cortex (10–14). Our second hypothesis was that placebo modulates activity of the pain matrix by creating expectations for pain relief, which in turn inhibit activity in pain-processing regions. Converging evidence suggests that the prefrontal cortex (PFC), the dorsolateral aspect (DLPFC) in particular, acts to maintain and appropriately update internal representations of goals and expectations, which modulate processing in other brain areas (15, 16). Thus, stronger PFC activation during the anticipation of pain should correlate with greater placebo-induced pain relief as reported by participants and greater placebo-induced reductions in neural activity within pain regions (17).

Placebo reduces reported pain and brain activity in Study 1 (shock pain).

The design of Study 1 is illustrated in Fig. 1A (see the figure legend for a description) (18). First, to confirm that application of shock elicited a neural response in pain-related areas, we compared brain activity in the intense shock versus no shock conditions. This revealed activation of the classic pain matrix (11, 14, 19, 20), including thalamus, primary somatosensory cortex/primary motor cortex (S1/M1), secondary somatosensory cortex (SII), midbrain, anterior insula, anterior cingulate cortex (ACC), ventrolateral prefrontal cortex, and cerebellum (fig. S1). As expected, activations in thalamus, S1, SII, and M1 were larger in the left hemisphere, contralateral to the wrist where shocks were applied, whereas cerebellar activation was ipsilateral, although some bilateral activation was observed in each of these areas. We also...
compared intense shock with mild shock to determine which pain regions responded more specifically to the painful aspects of the stimulus, which produced a similar network of activated regions (Fig. 1C and table S1). These regions, which we refer to as “pain-responsive” regions because they track the magnitude of painful stimulation (10), constituted the pain-sensitive regions of interest (ROIs) in which we expected to find placebo effects (21). Anticipation of shock activated contralateral S1, SII, M1, and dorsal amygdala (fig. S2).

Turning to placebo effects, we first assessed the placebo effect based on participants’ reports, calculated as the difference between the average rating of intense shocks in the placebo and control conditions. Reported pain was greater for control shocks in the placebo and control conditions (control – placebo effect) correlated with the magnitude of reduction in neural activity during the shock period (control > placebo, a measure of placebo analgesia in the brain) in pain-responsive portions of several brain structures. These structures included the rostral anterior cingulate cortex (ACC), DLPFC and orbitofrontal cortex (OFC), secondary somatosensory cortex; INS: insula; TH: thalamus.

During the calibration phase, the stimulus was varied to identify temper-atures corresponding to reported pain levels of 2, 5, and 8 on a 10-point scale (1 = just painful; 10 = unbearable pain) for each participant (59). This was followed by the manipulation phase, included to enhance participants’ expectations of pain relief and thereby increase placebo responding. In this phase, pain was surreptitiously reduced in the placebo condition (10, 50). During one block of trials the stimuli were applied to the placebo-treated patch of skin, and during another block the stimuli were applied to the control-treated patch (order counterbalanced across participants). Participants were told that all stimuli were at level 8. However, they were administered at level 2 in the placebo-treated patch and at level 8 in the control-treated patch. Finally, during the test phase, two additional blocks of stimuli were administered to placebo- and control-treated patches of skin. Again, participants were told these were at level 8, but both were delivered at level 5, in keeping with the paradigm used in (5). Because the stimuli were identical, any differences in reported pain (control – placebo) during this phase are attributable to placebo effects. (C) Pain-responsive regions, identified by their significance in [intense – mild stimulation] contrasts in Study 1 or Study 2. These regions were ROIs in which we looked for placebo effects. ACC: anterior cingulate; rACC: rostral anterior cingulate; SII: secondary somatosensory cortex; INS: insula; TH: thalamus.
based on our hypothesis. OFC is thought to play an important role in configuring control mechanisms and learning based on reward information (26–31). Regions within bilateral DLPFC showed significant correlations ($r = 0.62$ within both left (L) and right (R) hemispheres) (32). Regions within bilateral OFC showed similar correlations (OFC; $r = 0.65/0.76$ in L/R hemispheres, respectively) (Fig. 3B) (32). Previous research (33) suggests that rACC may also serve as a control region, because it was activated in placebo relative to control conditions. Our data support this notion, as we also found correlations of the form described above for rACC (32). Correlations between reported placebo effects and prefrontal activation are consistent with the hypothesis that regions in generating and maintaining expectations contribute to placebo-related analgesia.

We also tested for correlations between anticipation activity in expectancy areas and pain activity in pain regions. Negative correlations would support the view that prefrontal activity is an antecedent to reduction in pain. Placebo-induced increases in DLPFC were correlated with placebo-induced reductions during pain in several regions: (i) contralateral thalamus, $r = -0.56/-0.38$ for L and R DLPFC; correlations whose absolute value is greater than 0.4 are significant at $P < 0.05$; (ii) insula, $r = -0.59/-0.26$ for L and R DLPFC; and (iii) rACC, $r = -0.44/-0.45$ for L and R DLPFC. Similar correlations were observed between placebo increases in OFC and placebo reductions in pain activity: (i) thalamus, $r = -0.52/-0.63$ for L and R OFC; (ii) insula, $r = -0.61/-0.56$ for L and R OFC; (iii) rACC: $r = -0.65/-0.70$ for L and R OFC.

We also found increased activity (placebo > control) during the anticipation period in the midbrain, in the vicinity of the periaqueductal grey (PAG), which contains a high concentration of opiate neurons with descending spinal efferents (23, 34). Midbrain placebo increases (placebo > control, at coordinates [10 -26 -14]) (35), were positively correlated with both reported placebo effects (control > placebo) and brain placebo effects (control > placebo) in some pain areas ($r = 0.47$ for thalamus and $r = 0.48$ for rACC) (36). Furthermore, midbrain placebo > control activity was correlated with anticipation-period activation (placebo > control) of the right PFC (r = 0.51) and OFC (r = 0.48/0.39 for L and R hemispheres) (37).

**Fig. 2.** Pain regions showing correlations between placebo effects in reported pain (control — placebo) and placebo effects in neural pain (control — placebo). (A) Rostral anterior cingulate (rACC) effects in Study 1. (B) rACC effects in early heat in Study 2. (C) Contralateral (left) insula (INS) in Study 1, z = -4 mm. (D) Contralateral (right) INS effects in Study 2, z = -4 mm. The parahippocampal cortex (PHCP) activations extended into the basal forebrain and are contiguous with thalamic activations; however, only thalamic activations are in pain-sensitive regions. (E) Contralateral INS and thalamus (TH) in Study 1, z = 6. (F) Contralateral INS and TH in Study 2, z = 6 mm.
insula and thalamus (Fig. 2, D and F), main effects of placebo (control > placebo) were found in the late heat period (43). Thalamic activations extended into the basal forebrain and medial temporal cortex (Fig. 2E), which has been implicated in enhanced pain due to anxiety (44). All these placebo activations fell within pain-sensitive regions, consistent with the hypothesis that they reflect modulation of the pain experience.

Time courses of neural placebo effects (Fig. 4) show the predominant decrease late in the pain response, after stimulus offset (although there is a trend toward control > placebo effects earlier in stimulation as well) (45). The late decreases suggest that placebo effects may require a period of pain to develop, and may modulate pain signals most strongly after stimulation is removed. This may be especially true of protracted painful stimuli, such as the thermal stimulus used in Study 2. The late decreases may reflect cognitive reappraisal of the significance of pain, resulting in decreases in pain affect and pain experience (5, 8). Alternatively, the late decreases may reflect engagement of opioid mechanisms triggered by prolonged pain.

Placebo increases prefrontal cortex and midbrain activity in anticipation of thermal pain. Study 2 also provided further support for our second hypothesis, that the expectation of pain relief is mediated by PFC. Regions within both right and left DLPFC, similar to those observed in Study 1 and shown in Fig. 3C, were significantly more active during anticipation in the placebo versus control conditions (placebo > control) (46). Study 2 also confirmed placebo-increased activation during the anticipation period of a midbrain region containing the PAG (46) (Fig. 3D), which again correlated significantly with DLPFC activity (r = 0.60 for both L and R DLPFC) (Fig. 3E). Finally, Study 2 showed the expected placebo-induced activation of rACC (47). Interestingly, this is the same area in which we found placebo-induced decreases during early heat, suggesting that this pain-responsive region may also serve as part of the network for cognitive control.

Overall impact of the studies. These two studies provide important insights into the neural mechanisms underlying placebo analgesia. First, they support the hypothesis that placebo manipulations decrease neural responses in brain regions that are pain sensitive. In addition, the magnitude of these neural decreases correlates with reduction in reported pain. These findings provide strong refutation of the conjecture that placebo responses reflect nothing more than report bias (6).

Our findings also provide support for a specific hypothesis regarding one potential mechanism of placebo action, the representation of expectations within regions of PFC that modulate activity in pain-responsive areas. We found significant correlations of DLPFC and OFC activity with placebo response, measured both behaviorally (as the reported experience of pain) and neurally (as activity in pain-responsive areas). The DLPFC is an area that has consistently been associated with the representation and maintenance of information needed for cognitive control (16, 48), whereas the OFC is more frequently associated with representing evaluative and re-
ward information relevant to the allocation of control (26, 27, 29).

Previously, Petrovic et al. (33) found increases in OFC in placebo during pain, whereas the current studies found it during anticipation (49). However, the Petrovic study used positron emission tomography and did not include an anticipation period, and so could not discriminate neural responses during anticipation from those associated with the painful stimulus itself. Nevertheless, it may be that the OFC is involved in processes that occur in advance of pain only if warning stimuli signal that pain is imminent, and otherwise occur during pain itself. Affective and motivational responses to pain are examples of such processes.

Both DLPFC and OFC activation correlated with midbrain activation during anticipation, consistent with the idea that prefrontal mechanisms trigger opioid release in the midbrain. An alternative interpretation is that DLPFC redirects attention away from pain, as it has also been implicated in general attentional processes (10, 50). However, OFC and midbrain regions are not typically associated with directed attention; rather, activation of these regions seems more consistent with the view that anticipation during placebo involves a specific expectancy process that may be related to opioid system activation. Although the results do not provide definitive evidence for a causal role of PFC in placebo, they were predicted by and are consistent with the hypothesis that PFC activation reflects a form of externally elicited top-down control that modulates the experience of pain.

The studies also provide additional information about which aspects of pain—sensory, affective, or cognitive evaluation—are affected by placebo. Previous studies showing reversal of placebo effects by opioid antagonists (2, 3), coupled with theories implicating opioids in the inhibition of spinal pain afferents (23), suggest that placebo affects sensory pain transmission at the earliest stages. Inhibition of spinal afferents might be expected to produce placebo decreases throughout the pain matrix; however, we found such reductions only in a few regions (table S1). Our findings provide evidence for multiple components of expectation-induced placebo effects, with (potentially) opioid-containing regions in the midbrain active during anticipation, anterior cingulate showing decreased responses early in pain, and thalamus and insula showing decreases only after more prolonged pain (Study 2). Although our results are consistent with the hypotheses that at least a part of the placebo effect is mediated by afferent pain fiber inhibition, a major portion of the placebo effect may be mediated centrally by changes in specific pain regions. This account acknowledges that pain is a psychologically constructed experience that includes cognitive evaluation of the potential for harm and affect as well as sensory components (24, 51).

References and Notes

17. Expectation generation is conceptually distinct from simple direction of attention away from painful stimuli, which has also been shown to modulate pain (52–55). The critical distinction is that expectation-induced analgesia should (i) engage prefrontal regions primarily during anticipation of pain; (ii) potentially activate opioid systems in the midbrain PAC; and (iii) activate affective regulation mechanisms in OFC and anterior medial PFC (56, 57). General attention effects, on the other hand, should be mediated by a distributed attentional network that remains active throughout pain and is not linked to affective regulation and/or opioid activity.
18. Materials and methods are available as supporting material on Science Online.
21. To avoid missing pain regions due to power issues, we defined stimulation-responsive (intense-none) and paired stimulation regions (intense-mild) as those that responded in these comparisons in either Study 1 or Study 2. This procedure also makes the pain masks comparable across the two studies.
22. Placebo effects in brain (control & placebo) that were positively correlated with experienced pain (control > placebo) in stimulation-responsive ROIs (defined by pain > baseline) included rACC ([4 23 27]), 27 contiguous voxels, Z = 3.56; and [−2 32 19], 16 voxels, Z = 3.12 and left (contralateral) insula ([−44 14 −3], 19 voxels, Z = 3.04). These activations overlapped with pain-responding ROIs (defined by intense-mild pain) in S, 5, and 8 voxels, respectively. Thalamic placebo effects were just below the 10-voxel extent threshold ([11 −5 14], 8 voxels, Z = 2.65, 3 voxels in pain-sensitive regions), but stronger support for thalamic involvement was found in Study 2.
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Fragmentation in Massive Star Formation

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Studies of evolved massive stars indicate that they form in a clustered mode. During the earliest evolutionary stages, these regions are embedded within their natal cores. Here we present high-spatial-resolution interferometric dust continuum observations disentangling the cluster-like structure of a young massive star–forming region. The derived protocluster mass distribution is consistent with the stellar initial mass function. Thus, fragmentation of the initial massive cores may determine the initial mass function and the masses of the final stars. This implies that stars of all masses can form via accretion processes, and coalescence of intermediate-mass protostars appears not to be necessary.

There is a general consensus that massive stars (>8 solar masses (M_⊙)) form exclusively in a clustered mode, but the detailed physical processes are far from clear. Although high enough accretion rates and accretion through disks are capable of forming massive stars, scenarios such as the merging of intermediate-mass protostars at the dense centers of evolving clusters are also possible (1–4). Furthermore, one needs to understand why the stellar clusters have a universal mass spectrum that is fairly independent of environmental conditions and how this mass spectrum evolves. Therefore, it is crucial to study the earliest evolutionary stages at high spatial resolution, preferably in the millimeter-wavelength regime, where dust emission is strong and optically thin, tracing all dust along the line of sight. The dust emission is directly proportional to the column density of dense gas within the regions; thus, observing the millimeter-continuum emission in very young massive star–forming regions allows us to study the gas and dust distributions, the possible fragmentation of the larger-scale cores, and physical parameters such as masses and column densities.

We recently imaged dust continuum emission at 1.3 and 3 mm from the massive star–forming region IRAS 19410+2336 with the Plateau de Bure Interferometer (PdBI (5)). The region IRAS 19410+2336 is in an early stage of high-mass star formation before forming a hot core—a dense hot clump of gas heated by a massive protostar (6). It is at a distance of ~2 kiloparsecs (kpc) and has an integrated bolometric luminosity of about 10^5 solar luminosities. The region is part of a large sample of high-mass protostellar objects that has been studied extensively at wavelengths ranging from centimeters to x-rays (7–11).

The PdBI consists of six 15-m antennas, and we have observed the source in three different configurations, with projected baseline lengths between 15 and 330 m. The two-dimensional representation of projected baselines on the plane of the sky—the uv plane—is covered extremely well in this range, providing high image fidelity at the corresponding spatial frequencies (12). At 1.3 mm, the synthesized beam is 1.5′′ × 1′′ and at 3 mm it is 5.5′′ × 3.5′′. Additionally, we present single-dish 1.2-mm observations of the same region obtained with the Institut de Radioastronomie Milimetrique (IRAM) 30-m telescope at 1′′ spatial resolution (8). Thus, we are able to analyze the evolving cluster at several spatial scales down to a linear resolution of 2000 astronomical units (AU; 1′′ at a distance of 2 kpc).

The large-scale emission observed at a wavelength of 1.2 mm with the IRAM 30-m telescope (Fig. 1A) shows two massive gas cores roughly aligned in a north-south direction. Based on the single-dish intensity profiles, we predicted that the cores should split up into substructures at scales between 3′′ and 5′′ (8). PdBI 3-mm data at more than twice the spatial resolution show that both sources split up into substructures at the previously predicted scales, about four sources in the southern core and four in the northern core (Fig. 1B). At the highest spatial resolution (Fig. 1, C and D), we observe that previously known gas clumps resolve into even more substructures. We find small clusters of gas and dust condensations with at least 12 sources per large-scale core. Each of the pro-

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